REMARKS

I. Preliminary Remarks

Applicants, through the undersigned attorney wish to thank the Examiner for the courtesy shown during the telephonic Interview conducted November 1, 2004. During that Interview amendments to the claims, the pending rejections under 35 U.S.C. §112 and the differences between the steps of the claimed method and those of the prior art references were discussed.

Independent claims 31, 35 and 36 are amended to remove the recitation of "antigen-independent" and claim 35 has been amended to replace the phrase "providing suitable host cells harboring a DNA library" with "transformation of suitable host cells with a nucleic acid library." In addition, the claims have been amended to recite that the method identifies intrabody frameworks and intrabodies "which are soluble and stable in selected conditions" and that the detection is by detection of a marker protein "wherein the detection of the marker protein is not dependent upon the presence of an antigen for which the intrabody is specific." In addition, claim 36 has been amended to replace the words "providing" and "harboring" with "transformation" or "express" respectively. Finally, new claims 45-47 are introduced which specify that the selected conditions are "reducing conditions."

These amendments are supported throughout the specification and do not introduce new matter to the case. As discussed at the Interview the recitation that "the detection of the marker protein is not dependent upon the presence of an antigen for which the intrabody is specific" is not present *ipsis verbis* within the specification. Nevertheless, the written description requirement is satisfied because one of ordinary skill in the art reviewing the disclosure would appreciate that Applicants disclosed performing the claimed assays in a manner wherein detection of the marker protein was not dependent upon an antigen-antibody interaction and considered this to be one aspect of their invention. While this is disclosed in

the text of the specification it is most clearly seen from an examination of Figures 1 and 2 which depict activation of the reporter gene through a cascade initiated by an intrabody **not bound to its corresponding antigen!**

It is also clear from the text of the specification that the initiation of this cascade is dependent upon the stability and solubility of the intrabody and not upon an antigen-antibody interaction as was known in prior art systems (including those cited in the Office Action). (See the specification at page 13, lines 12-14: "wherein said marker system is only activated in the presence of a fusion protein encoding a soluble and stable intrabody framework...") In contrast, traditional two-hybrid systems such as those of Visintin (see Fig. 1) and of Taliana (see Fig. 1) clearly rely upon binding antibody to antigen to activate a reporter gene.

The test for written description is whether the disclosure itself makes clear that the Inventors were in possession of their presently claimed invention at the time of filing and an examination of the text and Figures of the application makes clear that this was the case.

During the Interview, the Examiner raised the issue of whether the claimed method was unpredictable because many intrabodies will not be soluble and stable under various given conditions. Applicants respond that because the claimed method is a screening method any unpredictability associated with the method is not inappropriate. While the results obtained by a screening method are by their very nature unpredictable (i.e., the methods screen unknowns for activity and one cannot predict the activity of a test sample before testing) the claimed method itself is reliable and no evidence has been presented that calls this reliability into question.

II. The Subject Matter of the Invention

The present invention is directed to methods for identifying intrabody frameworks that are stable and soluble in the intracellular environment.

Previously, intrabodies were produced from monoclonal antibodies and were selected with classical techniques such as phage display. Although successful intrabodies were described, it was unpredictable whether any particular intrabody would be functional within a cell. This did not relate so much to the binding affinity of the scFv for the target antigen but rather to the stability and solubility of the intrabody in the intracellular environment which was necessarily different from that in which they were produced. (*e.g.*, phage display and other classical techniques were performed under oxidizing conditions while the intrabodies must function under reducing conditions.) Such a reducing environment can lead to insufficient solubility of the intrabody resulting in non-functional aggregates, despite selection in a phage display method. Accordingly, the value of mRNA derived libraries of different scFv fragments is limited in the identification of CDRs which have a high affinity for the antigen because the corresponding framework may be insoluble and tend to aggregate.

Nevertheless, because the solubility of an intrabody can be modified by either changes in the framework or the CDR's, there is value in determining whether the intrabody will be soluble and stable independent of the binding affinity of the scFv for an antigen.

The methods of claims 31, 35 and 36 are therefore based on the finding that the solubility/stability of a fusion protein comprising a marker protein and an intrabody is dependent on the solubility/stability of the intrabody moiety. Thus, if the intrabody moiety is soluble and stable in the intracellular environment then the marker protein can be detected and cells expressing such a stable fusion protein can be selected. These methods do not involve any interaction between a scFv and its corresponding antigen.

III. The Outstanding Rejections

Claims 31, 33-38 and 42-44 stand rejected under 35 U.S.C. §112(first paragraph) for failure to comply with the written description requirement.

Claims 31 and 33-38 stand rejected under 35 U.S.C. §112(second paragraph) as being indefinite.

Claims 31, 33-38 and 43-44 stand as being anticipated under 35 U.S.C. §102(a) by Worn et al., Journal of Biological Chemistry, 275, No. 4 pp 2795-2803 (January 28, 2000)

Claims 31, 33-38 and 43-44 also stand as being anticipated under 35 U.S.C. §102(a) by Taliana et al., Journal of Immunological Methods, 238, pp 161-172 (2000).

Claims 31 and 33-38 stand rejected as being anticipated under 35 U.S.C. §102(a) by Visintin et al. PNAS, 96(21):112723-11728 (October 12, 1999).

Claim 42 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Worn or Taliana or Visintin et al. in view of Ptashne et al U.S. Published Patent Application No. 2004/0014036.

III. Patentability Arguments

A. The Rejections Under 35 U.S.C. §112 (First Paragraph) Should Be Withdrawn.

The written description rejections under 35 U.S.C. §112 (first paragraph) should be withdrawn in light of the amendments to the claims made herein. For example, claims 31-38 and 42-44 have been rewritten to delete the recitation of "antigen-independent." Instead claims 31 and 35 (but not claim 36) have been amended to recite that "the detection of the marker protein is not dependent upon the presence of an antigen for which the antibody is specific." Written descriptive support for these amendments is provided in Figs. 1 and 2 and throughout the text of the specification as discussed in detail above. Claim 36 recites that the first protein and second protein interact with each other "via a constant region of the first protein" and thus excludes an antigen/antibody interaction. Similarly, claim 35 has been rewritten to replace the recitation of "providing suitable host cells harboring a DNA library" with "transformation of suitable host cells with a nucleic acid library." Further, claim 36 has been amended to substitute "transformation" and "express" respectively for "providing" and

harboring." These amendments are supported by written descriptive support in the specification and do not introduce new matter.

B. The Rejections Under 35 U.S.C. §112 (Second Paragraph) Should Be Withdrawn.

The rejections under 35 U.S.C. §112 (second paragraph) for indefiniteness should be withdrawn in light of amendment of the claims. As noted above, "harboring" has been replaced with "transformed" and "providing" has been deleted.

In response to the query regarding how the host cells can produce first and second proteins the Examiner is directed to the discussion throughout the specification and particularly at page 13, line 31 through page 14, line 18 at which different variations are described. One such variation includes that wherein the library encoded proteins comprise a transcriptional activation (AD) domain (see Fig. 1A) and said second proteins comprise a DNA binding domain or vice versa. It is submitted that those of ordinary skill in the art would understand the designation of first and second proteins in the context of two-hybrid detection systems.

C. The Rejections of Claims 31-38 Under 35 U.S.C. §102 Should Be Withdrawn.

The present invention is directed to methods for the identification of intrabody frameworks or intrabodies which are soluble and stable which methods do not involve any interaction between the antibody and its corresponding antigen. The rejections over each of the cited art references should be withdrawn because all those methods involve an interaction between the antibody and its corresponding epitope of the antigen. Thus, each of Visintin, Taliana and Worn rely upon an antigen-antibody interaction to perform their assay. This reliance creates disadvantages in those methods because a tested intrabody or intrabody framework might be stable and soluble but it will not be detected if its CDR lacks good antigen binding activity. Thus, in the absence of an antigen-antibody interaction, the

Visintin, Taliana or Worn assays are susceptible to providing falsely negative results regarding the stability of the intrabody framework because of the failure of antigen-antibody binding.

1. The Section 102 Rejection over Worn et al. Should be Withdrawn.

The rejection of claims 31, 33-35 and 43-44 under 35 U.S.C. §102(a) over Worn et al should be withdrawn because that reference discloses an assay method in which the detection of a marker protein is dependent upon the interaction of antibody with antigen. See Worn at page 2796, left column, in which the system was used to investigate the correlation between "*in vitro* stability ... antigen affinity, and *in vivo* inhibition of Gen4p..." (emphasis supplied)

2. The Section 102 Rejection Over Taliana et al. Should be Withdrawn.

The rejection under 35 U.S.C. §102(a) over Taliana et al should also be withdrawn because that reference is directed to a method for the isolation of scFv in yeast cells using a two hybrid system which relies upon an antigen dependent interaction between the scFv and its corresponding antigen (See Taliana Figure 1 and compare to Applicants' Figure 1). In this case, it is the antigen-antibody interaction which activates the marker protein.

3. The Section 102 Rejection Over Visintin et al. Should be Withdrawn.

The rejection of claims 32, 33-38 and 43-44 under 35 U.S.C. §102(a) over Visintin et al. should also be withdrawn because Visintin also relies upon the use of the two hybrid system for the isolation of intrabodies using an antibody/antigen interaction wherein the claimed identification of the intrabodies is based on the antigen dependent interaction between the antibody and its corresponding antigen. An examination of Figure 1 of Visintin et al. shows that the two-hybrid method was adapted "to detect antibody-antigen interaction *in vivo*." Thus, "[i]f antibody-antigen interaction occurs, *in vivo*, the resulting complex can bind to the LexA DBS upstream of *his* or *lacZ* genes" resulting in either growth of the

transformed yeast or expression of a visible signal, respectively.) Again, a comparison of Figure 1 of Visintin with Applicants' Figure 1 is solicited.

D. The Rejection of Claim 42 Under 35 U.S.C. §103 Should Be Withdrawn.

The rejection of claim 42 under 35 U.S.C. §103(a) over any of Worn or Taliana or Visintin in further view of Ptashne et al., U.S. 2003/0017149 should be withdrawn because Ptashne too uses a two hybrid system relying upon a direct antibody-antigen interaction for the identification and isolation of intrabodies. Thus, Ptashne fails to provide any motivation to modify the systems disclosed by each of Worn, Taliana or Visintin to provide the claimed invention.

CONCLUSION

For the foregoing reasons it is submitted that each of claims 31, 33-38 and 42-47 should now be allowed. Should the Examiner wish to discuss any issues of form or substance in order to expedite allowance of the pending application, she is invited to contact the undersigned at the number indicated below.

The Commissioner is authorized to charge any fee deficiency required by the paper to Deposit Account No. 13-2855.

Respectfully submitted,

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